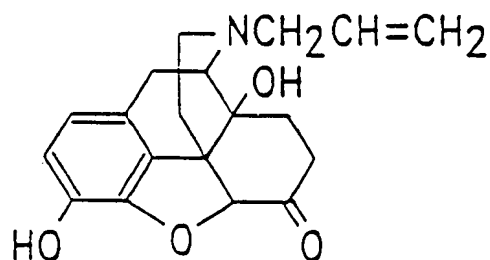
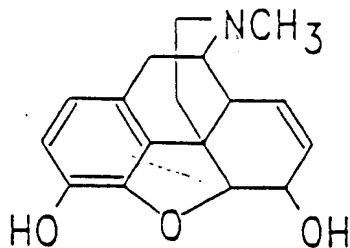
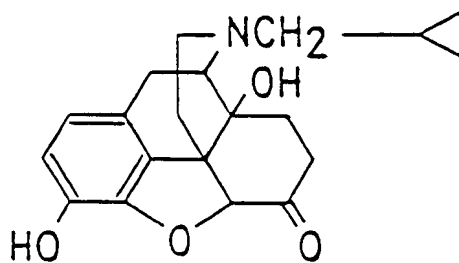


APPROVED	O.G. FIG. —
BY	CLASS SUBCLASS
DRAFTSMAN	514 285

Morphine



Naloxone



Naltrexone (R=O)  
Nalmefene (R=CH<sub>2</sub>).

FIG. 1

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APPROVED	O.G. FIG. —
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4. Et 1nM
5. Et 1uM
6. BSS

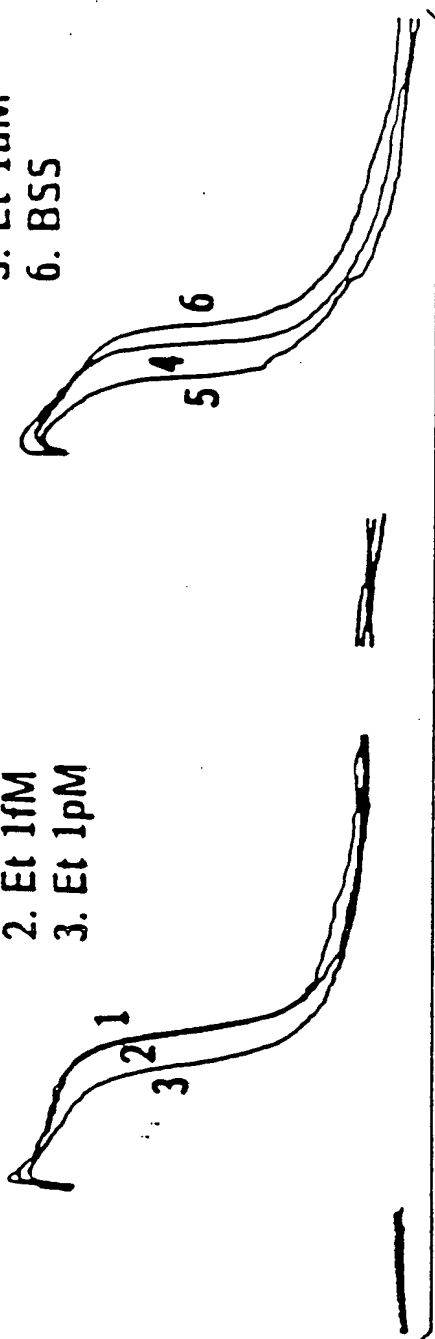


FIG. 2A

3. NLX 10nM
4. NLX + Et 1nM
5. NLX + Et 1uM

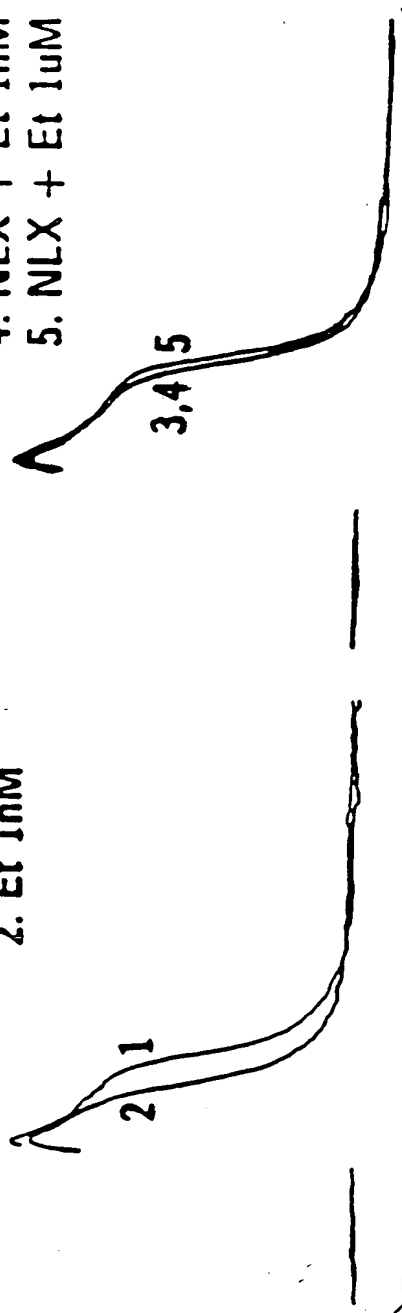
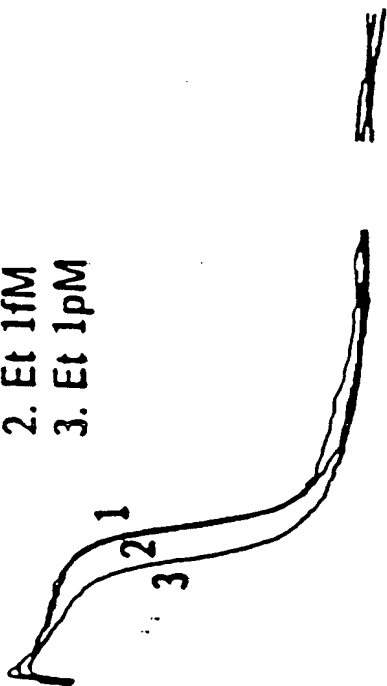
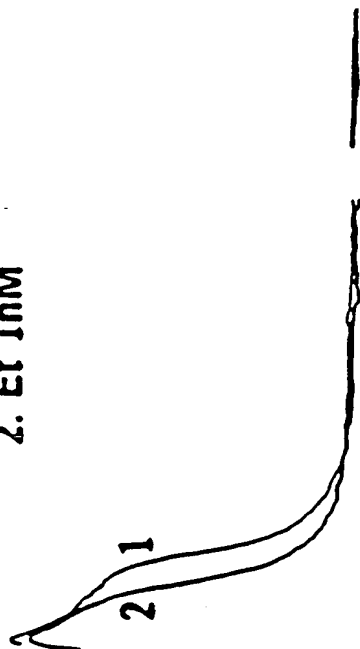


FIG. 2B

1. BSS
2. Et 1fM
3. Et 1pM



1. BSS
2. Et 1nM



20EOTD" T644EOT

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
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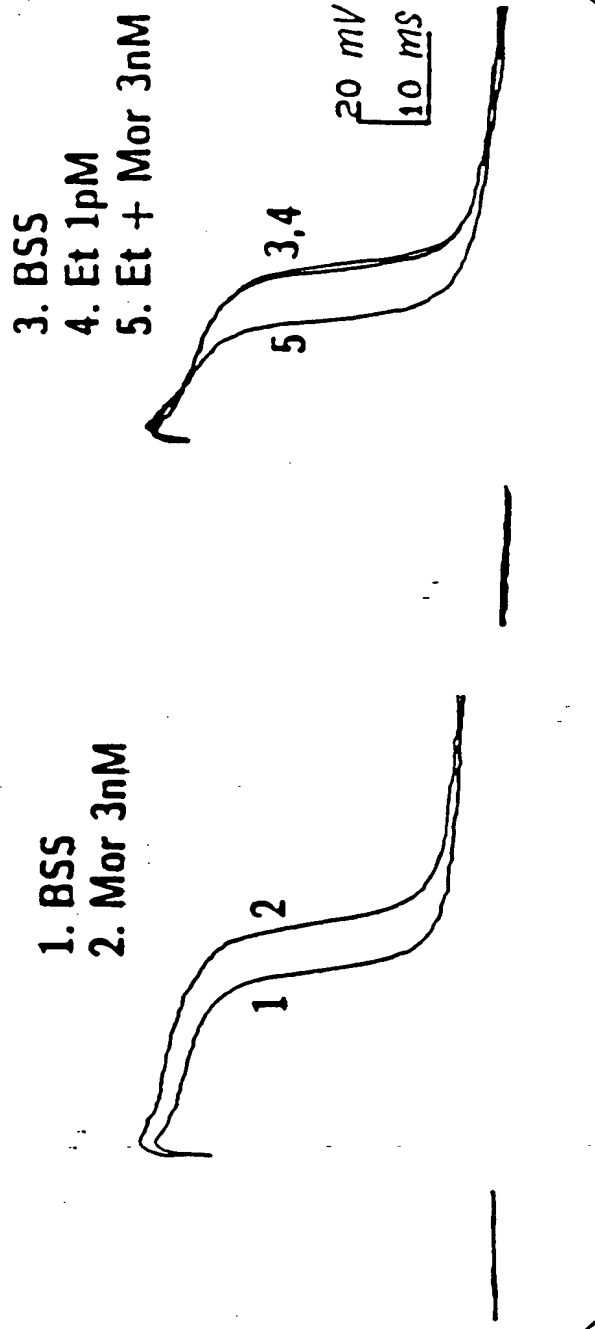


FIG. 2C

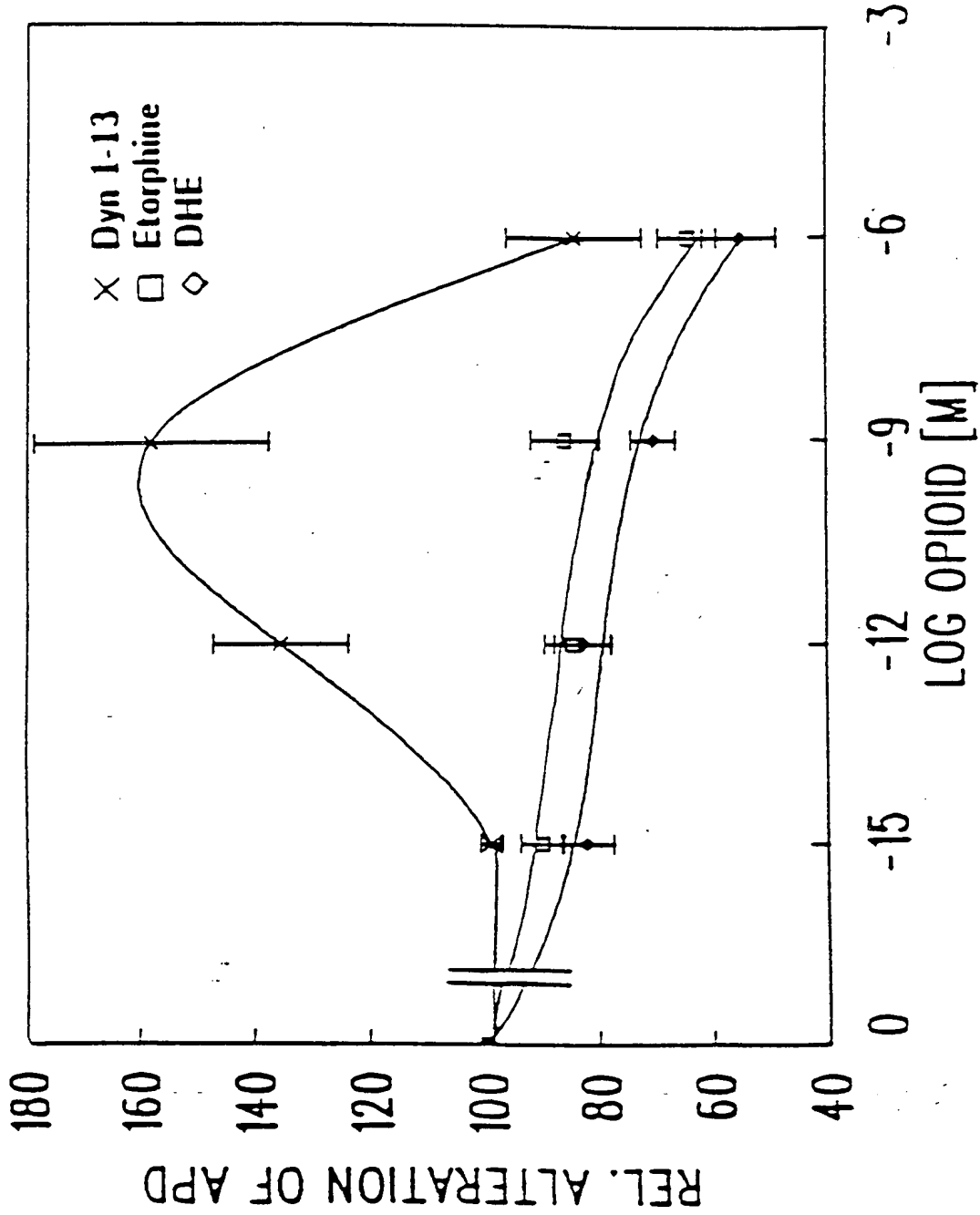
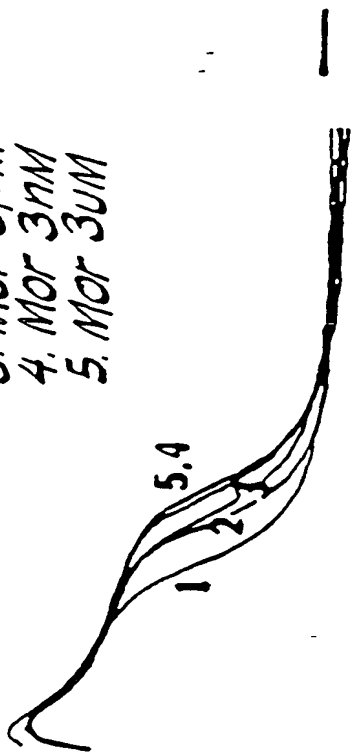


FIG. 3

APPROVED	O.G. FIG. —
BY	CLASS
DRAFTSMAN	SUBCLASS
574	285

1. BSS
2. MOR 3fM
3. MOR 3pM
4. MOR 3nM
5. MOR 3uM



6. BSS
7. DPN 1pM
8. DPN + MOR 3fM
9. DPN + MOR 3pM
10. DPN + MOR 3nM
11. DPN + MOR 3uM

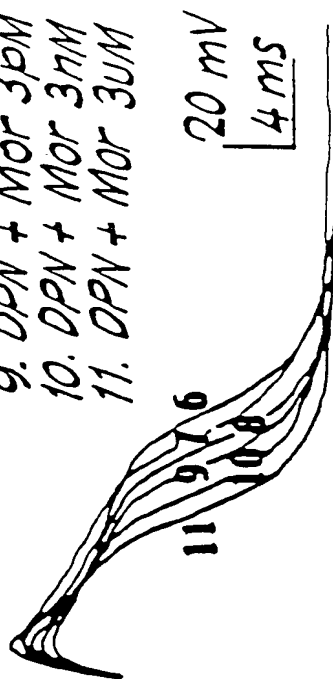
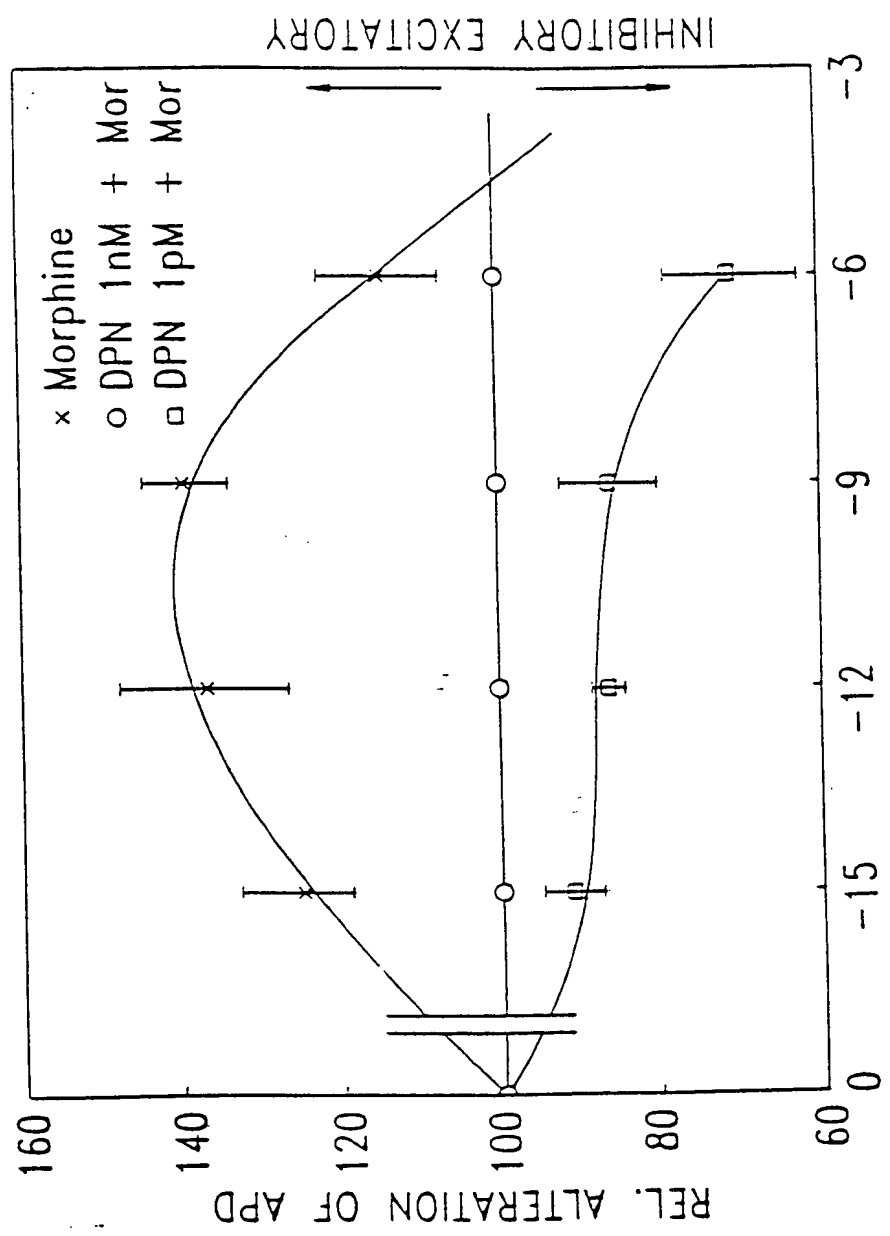


FIG. 4A

202010" T644E00T

APPROVED	OG. FIG. —	
BY	CLASS	SUBCLASS
DRAFTSMAN	T14	285



20E07D-T644E00T

APPROVED	O.G. FIG. —	
BY	CLASS	SUBCLASS
DRAFTSMAN	716	285

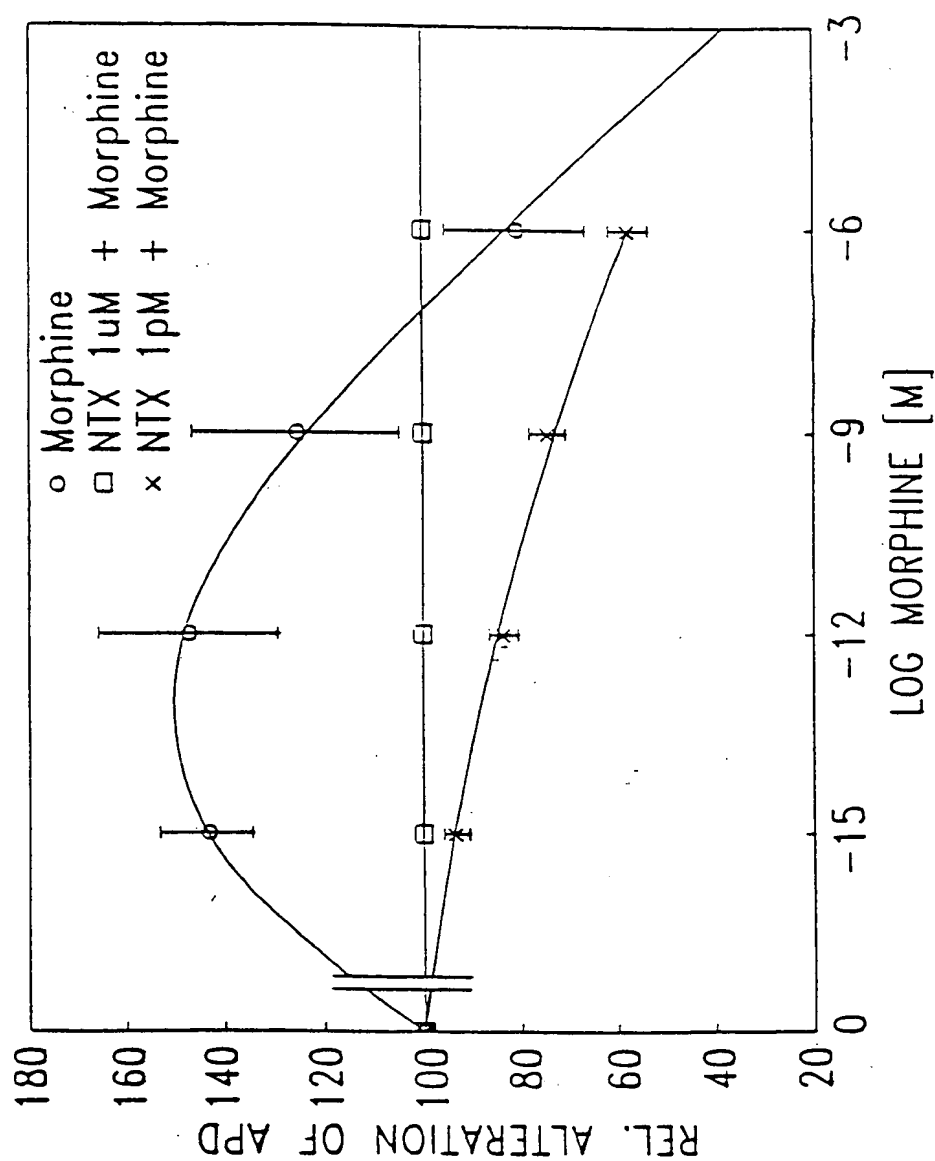


FIG. 5

20200707 164400

Alteration of Action Potential Duration (APD)				
(APD shortening: ↓ ; APD prolongation: ↑ ; No APD change: 0)				
Acute Test	Naive DRG Neurons		Chronic Morphine-Treated Neurons (1μM; >1wk)	Chronic Co-treatment with Mor + Antag. at Excit. Op. Rec. (pM)
	Control BSS	BSS + Antag. at Excit.Op.Rec. (pM)	After Washout with BSS	
1 - 10 μM morphine	↓ (inhibitory) ("analgesia")	↑↑	↑ ("tolerance")	↑
pM - nM morphine	↓ ("excitatory antianalgesia")	↓ (unmasking of inhibitory effects)	↑	↑
~ fM morphine or dyn A-(1-13)	0	0	↓ (excitatory supersensitivity)	0
nM naloxone	0	0	↓ ("dependence") ("withdrawal effect")	0

FIG. 6

APPROVED	O.G. FIG. —
BY	CLASS
DRAFTSMAN	SUBCLASS
714	285

Co-Treatment with Low-dose Naltrexone Enhances  
Morphine's Antinociceptive Potency

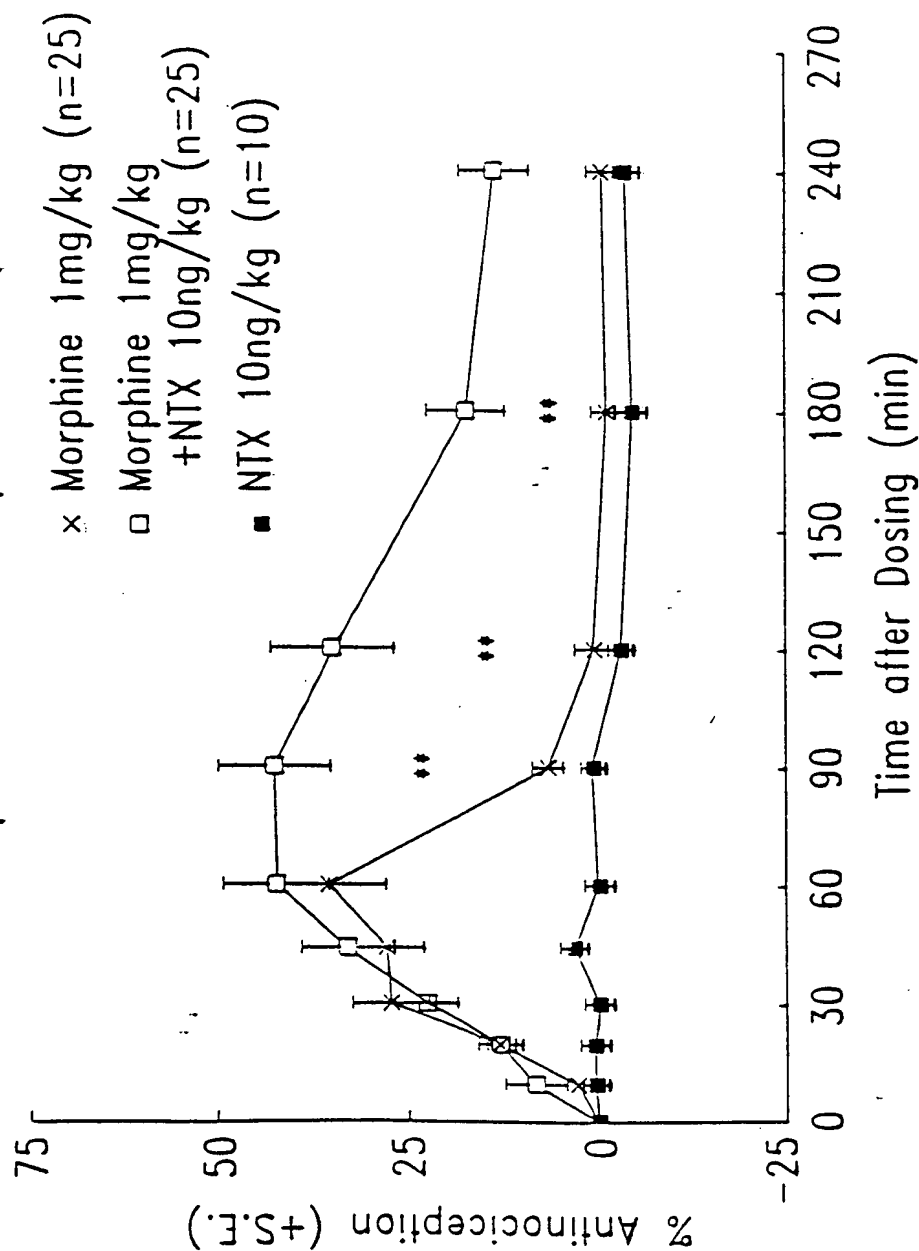


FIG. 7

# Co-Treatment with Low-Dose Naltrexone Attenuates Acute and Chronic Morphine Dependence

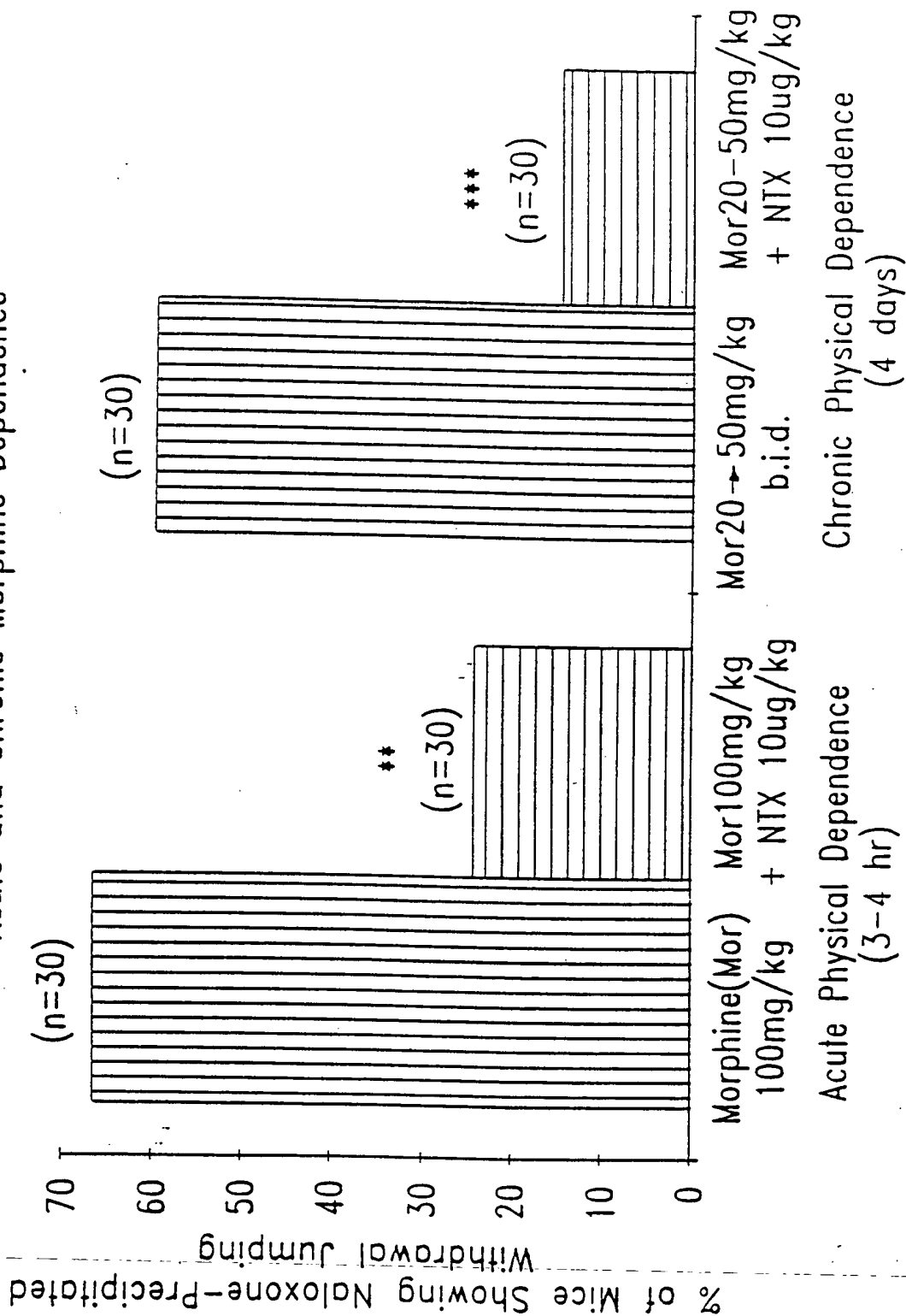


FIG. 8

APPROVED	O.G. FIG. —	
BY	CLASS	SUBCLASS
DRAFTSMAN	574	28.5

# Co-Treatment with Ultra-Low Dose Nalmefene Enhances Morphine Antinociceptive Potency

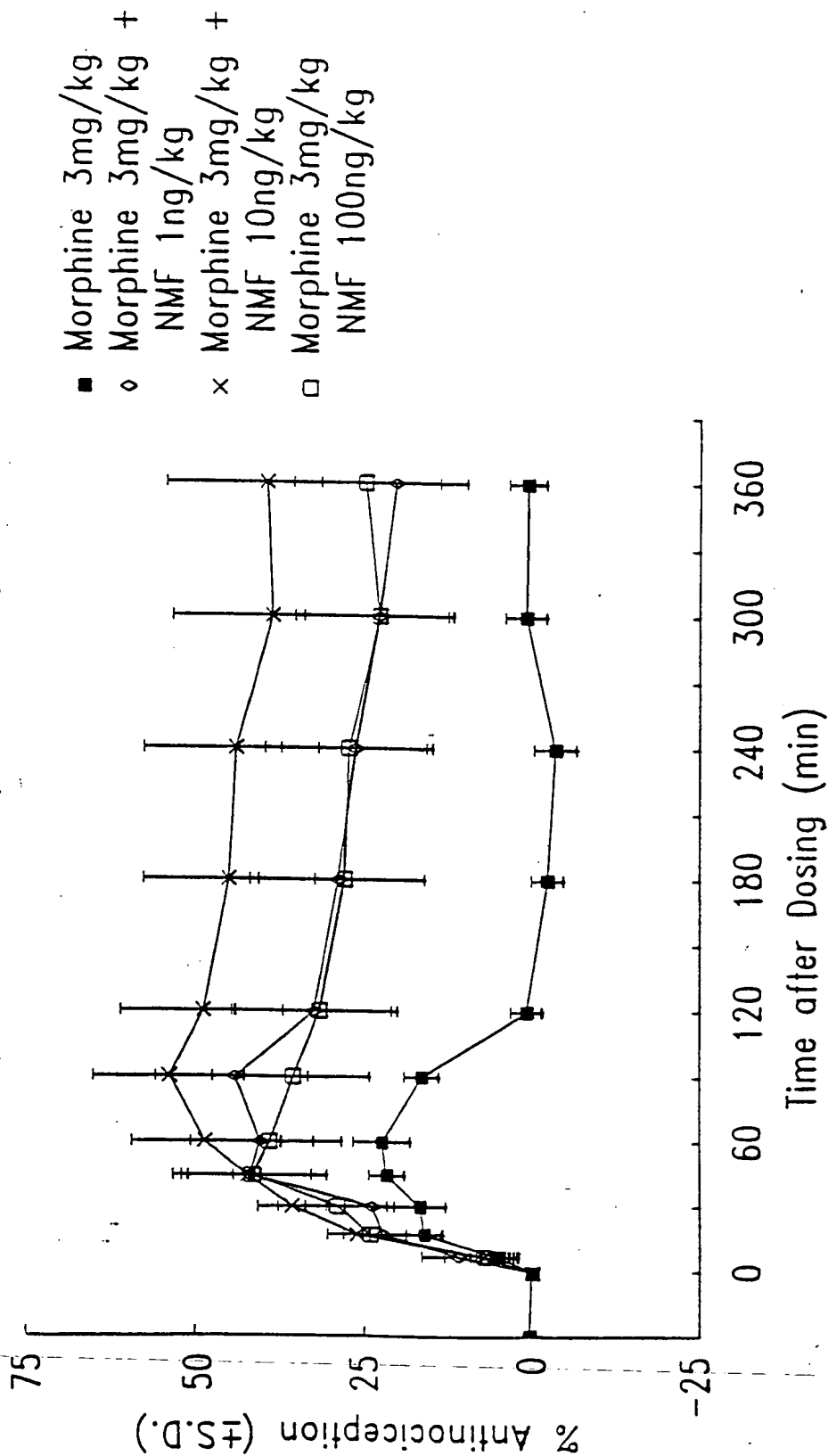


FIG. 9

20E0T0" T644E00T

APPROVED	O.G. FIG.	—
BY	CLASS	SUBCLASS
DRAFTSMAN	514	285

Co-Treatment with Low-Dose Naltrexone or Nalmefene  
Attenuates Acute Morphine Dependence

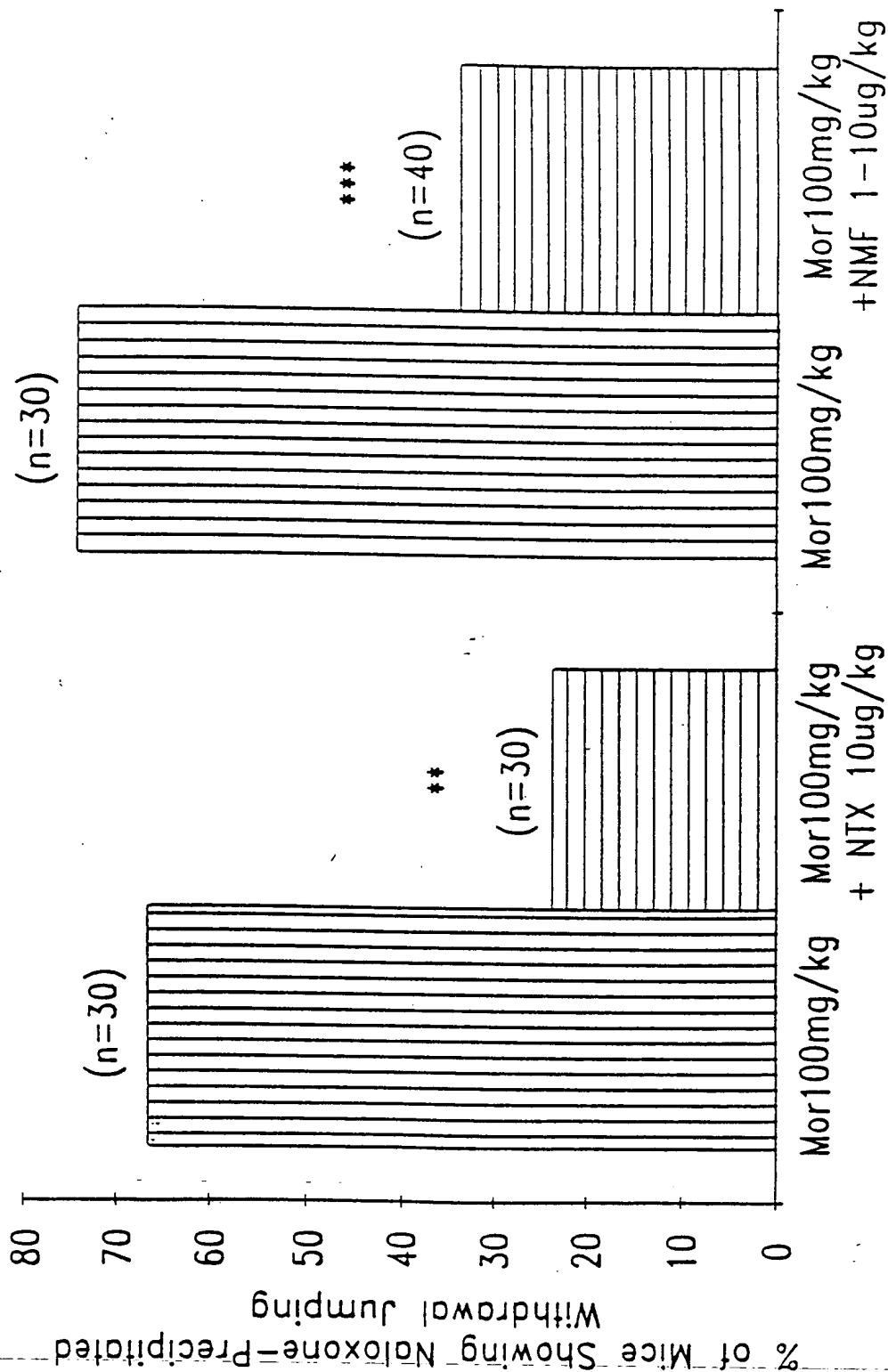


FIG. 10